MAJOR ARTICLE

Re-Evaluating the Treatment of Nongonococcal Urethritis: Emphasizing Emerging Pathogens–A Randomized Clinical Trial

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Background. Nongonococcal urethritis (NGU) is a common chlamydia-associated syndrome in men; however, *Trichomonas vaginalis* and *Mycoplasma genitalium* are associated with its etiology and should be considered in approaches to therapy. We sought to determine whether the addition of tinidazole, an anti-trichomonal agent, to the treatment regimen would result in higher cure rates than those achieved with treatment with doxycycline or azithromycin alone. A secondary aim was to compare the efficacy of doxycycline therapy and with that of azithromycin therapy.

Methods. Randomized, controlled, double-blinded phase IIB trial of men with NGU. Participants were randomized to receive doxycycline plus or minus tinidazole or azithromycin plus or minus tinidazole and were observed for up to 45 days.

Results. The prevalences of *Chlamydia trachomatis*, *M. genitalium*, and *T. vaginalis* were 43%, 31%, and 13%, respectively. No pathogens were identified in 29% of participants. Clinical cure rates at the first follow-up visit were 74.5% (111 of 149 patients) for doxycycline-containing regimens and 68.6% (107 of 156 patients) for azithromycin-containing regimens. By the final visit, cure rates were 49% (73 of 149 patients) for doxycycline-containing regimens and 43.6% (68 of 156 patients) for azithromycin-containing regimens. There were no significant differences in clinical response rates among the treatment arms. However, the chlamydia clearance rate was 94.8% (55 of 58 patients) for the doxycycline arm and 77.4% (41 of 53 patients) for the azithromycin arm ($P = .011$), and the *M. genitalium* clearance rate was 30.8% (12 of 39 patients) for the doxycycline arm and 66.7% (30 of 45 patients) for the azithromycin arm ($P = .002$).

Conclusions. Addition of tinidazole to the treatment regimen did not result in higher cure rates but effectively eradicated trichomonas. Clinical cure rates were not significantly different between patients treated with doxycycline and those treated with azithromycin; however, doxycycline had significantly better efficacy against Chlamydia, whereas azithromycin was superior to doxycycline for the treatment of *M. genitalium*.

Urethritis in males that is not caused by gonorrhea is classified as nongonococcal urethritis (NGU). NGU is the most common urethritis syndrome seen in men in the United States; in the past, p to 40% of NGU cases were attributed to *Chlamydia trachomatis*, and as many as 40% of cases were of unknown etiology [1–3]. However, there has not been a comprehensive re-evaluation of the therapy for NGU in 15 years [4]. Since that time, there have been data suggesting that additional pathogens may play an important role in the etiology of NGU and should be considered in approaches to therapy. Newer studies using more-sensitive diagnostic techniques have implicated other pathogens in the etiology of NGU including *Mycoplasma genitalium* and *Trichomonas vaginalis* [5, 6]. We hypothesized that currently recommended initial therapies for NGU, doxycycline and azithromycin, might be improved by the addition of antimicrobial coverage for *T. vaginalis*. We further hypothesized that, of the 2 currently recommended initial treatment regimens for NGU, azithromycin therapy would result in a higher

Received 27 July 2010; accepted 17 September 2010.

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Clinical Infectious Diseases 2011;52(2):163–170

1058-4838/2011/522-0001$37.00
DOI: 10.1093/cid/ciq074

clinical cure rate than doxycycline therapy because azithromycin, compared with doxycycline, apparently has greater efficacy against *M. genitalium* [7] and is reported to have equivalent efficacy against *C. trachomatis* [4].

METHODS

We conducted a randomized, controlled, double-blinded phase IIB treatment study of NGU. The primary aim was to determine whether the addition of tinidazole, a proven antitrichomonal agent [8], to the recommended treatment regimen for NGU [9] would be tolerable and more efficacious than treatment with either doxycycline or azithromycin alone. Tinidazole was chosen over metronidazole because of the former's superior penetration into the male genital tract tissues [10]. A secondary aim was to compare doxycycline treatment with azithromycin treatment for NGU with respect to the effect of each treatment drug on *M. genitalium*. This aim was motivated by accumulating data suggesting that doxycycline may lack clinical efficacy against *M. genitalium*, which plays a prominent role in the pathogenesis of NGU.

The study evaluated the efficacy of doxycycline administered in a 100-mg oral dose twice daily for 7 days plus or minus tinidazole administered in a single 2-g oral dose and the efficacy of azithromycin administered in a single 1-g oral dose plus or minus tinidazole administered in a single 2-g oral dose.

Study participants were heterosexual men 16–45 years of age who attended sexually transmitted disease (STD) clinics in Birmingham, Alabama; New Orleans, Louisiana; Durham, North Carolina; and Baltimore, Maryland. NGU was defined as new-onset urethral discharge or dysuria and a urethral smear with $\geqslant$5 polymorphonuclear leukocytes (PMNs) per 3–5 oil immersion fields without evidence of gonorrhea [9]. Participants were excluded from the study for the following reasons: a test result positive for gonorrhea at the baseline visit; history of recurrent NGU ($\geqslant$3 episodes within the previous year) or history of recent NGU (within the previous 30 days); signs or symptoms of epididymitis or prostatitis; known allergy to study drugs; receipt of systemic antibiotics within 30 days of enrollment; presence of concomitant infection that required antibiotics; unwillingness to abstain from alcohol for 24 h after enrollment; serious underlying infection, including known HIV infection or other primary or secondary immunosuppression; or voided within the hour preceding evaluation.

After consent was obtained, participants were asked questions regarding their sexual history and current symptoms. The presence of urethral discharge was confirmed. A urethral swab specimen was obtained for *T. vaginalis* nucleic acid amplification testing (NAAT), and a first fraction urine specimen was obtained for gonorrhea, chlamydia, *M. genitalium,* and *T. vaginalis* NAAT. Participants were asked to abstain from sexual intercourse or use condoms during the study period. Participants who tested positive for *Neisseria gonorrhoeae* were notified to return immediately for treatment according to local guidelines and were discontinued from the study.

Participants were randomized using a block randomization scheme with blocks of size 16 stratified by clinical center to 1 of 4 treatment arms: (1) doxycycline, (2) doxycycline plus tinidazole, (3) azithromycin, or (4) azithromycin plus tinidazole. The single doses of tinidazole and azithromycin (active or placebo) were directly observed. Participants were counseled regarding partner notification and treatment as well as abstinence and condom use.

Participants were asked to return in 1 week after completion of therapy (days 15–19). They were queried regarding interim sexual activity, symptoms, and possible adverse effects of the study medication. A genital examination was performed to determine the presence or absence of urethral discharge. Two urethral swab specimens were obtained for staining and quantifying PMNs on the urethral smear and for *T. vaginalis* PCR. A urine specimen was obtained for detection of *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, and *M. genitalium.* Participants with persistent symptoms and objective signs of NGU were discontinued from the study and treated according to local guidelines for recurrent or persistent urethritis. The final study visit was conducted during days 35–45 using the same procedures.

Definition of clinical cure varied slightly according to the study visit and was modeled after definitions used by Stamm et al [4] in the last major study of NGU treatment, which served as the historical benchmark for this study. At the first follow-up visit, clinical failure was defined as persistent symptoms and $>$5 PMNs per 3–5 oil immersion fields on the urethral smear (regardless of urethral discharge) or persistent urethral discharge on examination (regardless of symptoms or number of PMNs). At the final study visit, clinical failure was defined as $>$5 PMNs per 3–5 oil immersion fields alone (regardless of symptoms or presence of urethral discharge) or persistent urethral discharge on examination (regardless of symptoms or number of PMNs). Participants who failed to return and/or were not evaluated for any reason were designated as unevaluable. Participants who met the criteria for clinical failure at any visit were discontinued from the study and added to the cumulative failures for the study. Efficacy was based on the last visit for which the person had a clinical response determined.

Microbiological Methods

Urethral Gram stains were performed at the clinic sites to quantitate PMNs and determine the presence or absence of gram-negative diplococci. At each clinical site, urine specimens were mixed and aliquoted into transport media for the assay for *N. gonorrhoeae* and *C. trachomatis*. This testing was performed in

accordance with the manufacturer's instructions using the licensed GEN-PROBE TMA assay (Aptima Combo II; Gen-Probe).

Detection of *M. genitalium* in urine was performed centrally at Louisiana State University using the GEN-PROBE TMA-HPA *M. genitalium* analyte-specific reagent assay (Gen-Probe). PCR testing for *T. vaginalis* was performed centrally at the University of Alabama at Birmingham, as previously described [11].

Sample Size Estimation

It was hypothesized that conventional therapy (with azithromycin or doxycycline) would be at least 70% effective. For each conventional therapy agent, the sample size was estimated using the Mantel-Haenszel-Cochran test without continuity correction to adjust for stratification across 4 clinical centers. With 75 patients in each arm, an improvement in clinical cure rate to 89% within each parallel trial could be detected between a conventional therapy arm minus tinidazole and the corresponding arm plus tinidazole at the 1-sided .05 significance level with power of .90. Sample size was determined on the basis of response at the last evaluable visit.

Statistical Methods

The primary analysis population for efficacy and safety was the modified intent-to-treat (MITT) population, which comprised all participants randomized who received at least 1 dose of study drug therapy or placebo. Confirmatory analyses were performed with the per protocol population ($n = 200$), which did not include participants who did not meet eligibility criteria ($n = 12$), had protocol deviations potentially affecting the primary endpoint ($n = 8$), or did not adhere to the protocol visit schedule ($n = 85$).

For each of the treatment groups, the binomial proportion and its 95% confidence interval were used to estimate clinical cure rate. The stratified Mantel-Haenszel-Cochran test was used to evaluate the addition of tinidazole to each conventional therapy and to compare the 2 conventional therapies across the 4 clinical sites (strata). For each treatment group, the prevalence and microbiological cure rate for each organism (*C. trachomatis*, *T. vaginalis*, and *M. genitalium*) were estimated using the binomial proportions and 95% confidence intervals. For microbiological cure rates, the overall group effect was assessed using χ^2 tests, and when significant, pairwise comparisons were made.

RESULTS

A total of 305 study participants were randomized and included in the MITT population, as follows: 76 received doxycycline, 73 received doxycycline plus tinidazole, 77 received azithromycin, and 79 received azithromycin plus tinidazole (Figure 1). The first subject was enrolled in November 2006, and the last follow-up visit was completed in April 2009.

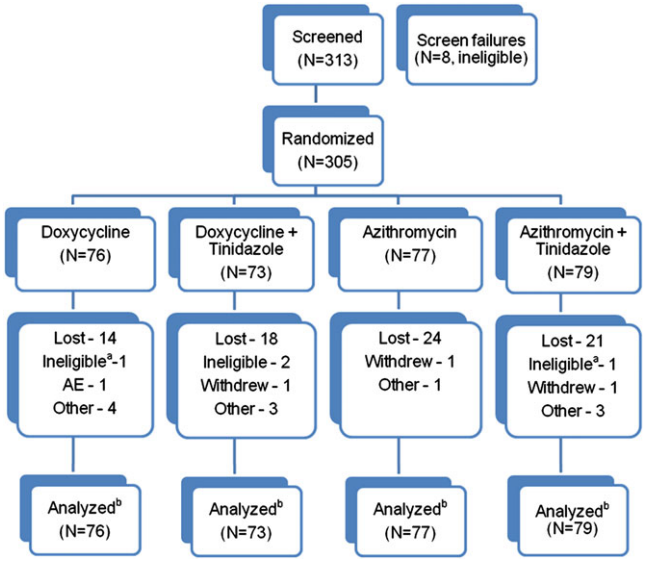

Figure 1. Study flow diagram. [a]The results of a gonorrhea test performed at screening were reported to be positive after randomization. [b]All randomized participants were analyzed in a modified intent-to-treat analysis.

The randomization groups were similar with respect to their baseline demographic characteristics and sexual history (Table 1). The median number of lifetime sexual partners was 20, whereas the median number of partners within the previous 30 days was 1. On average, 7 days had elapsed between the last time that participants had engaged in sexual activities and the time they presented for care. In terms of symptoms, 55% presented with urethral discharge only, 5% presented with dysuria only, and 40% presented with both discharge and dysuria.

Screening, Enrollment, and Follow-up

Of the 313 individuals screened for the protocol, 305 (97%) were enrolled. Of the 8 individuals who were eliminated at screening, 2 had gonorrhea and 6 did not have ⩾5 PMNs on urethral smear (1 of whom also did not have the required symptoms). Eighty-two percent of study participants completed the first follow-up visit, and 56% completed the second follow-up visit. Of those who discontinued the study early, 41% discontinued because of clinical failure at the first follow-up visit; having reached a specified study end point, their study discontinuation was in accordance with the protocol. Most of the other participants who terminated study participation before completing the second follow-up visit were lost to follow-up. The percentage of patients who were lost to follow-up varied by clinic and ranged from 15% at the Birmingham site to 42% at the New Orleans site, but this rate did not differ significantly according to treatment arm, with rates of loss to follow-up ranging from 18% for the doxycycline arm to 31% for the azithromycin arm.

Table 1. Baseline Participant Demographic Characteristics and Sexual History

Variable	Doxycycline therapy arm (n = 76)	Doxycycline + tinidazole therapy arm (n = 73)	Azithromycin therapy arm (n = 77)	Azithromycin + tinidazole therapy arm (n = 79)	All participants (n = 305)	P[a]
Age, mean years (±SD)	27.3 ± 7.0	27.8 ± 6.8	26.4 ± 6.7	25.7 ± 7.2	26.8 ± 6.9	.243
Race	74 (97)	72 (99)	76 (99)	77 (97)	299 (98)	
Black or African American						.953
White/other	2 (3)	1 (1)	1 (1)	2 (3)	6 (2)	
Education level	19 (25)	13 (18)	16 (21)	21 (27)	69 (23)	
No high school degree	.543					
Vocational, technical, or trade school certificate	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	
High school graduate or GED	33 (43)	35 (48)	39 (51)	34 (43)	141 (46)	
Some college	17 (22)	22 (30)	21 (27)	22 (28)	82 (27)	
Bachelor's degree or higher	6 (8)	3 (4)	1 (1)	2 (3)	12 (4)	
New sexual partners in previous 30 days, median no. of partners (range)	0 (0–3)	0 (0–3)	0 (0–4)	0 (0–27)	0 (0–27)	.738
Episodes of vaginal sex in the previous 30 days, median no. of episodes (range)	5 (0–40)	5 (0–50)	4 (0–90)	5 (0–30)	5 (0–90)	.962
Episodes of receptive oral sex in the previous 30 days, median no. of episodes (range)	2 (0–30)	1 (0–30)	2 (0–90)	2 (0–30)	2 (0–90)	.674
Different sexual partners in the previous 3 months, median no. of partners (range)	2 (1–6)	2 (0–20)	2 (0–30)	2 (1–100)	2 (0–100)	.297
Condom use during most recent sexual encounter	48 (63)	51 (70)	48 (62)	39 (49)	186 (61)	
No						.066
Yes	27 (36)	22 (30)	29 (38)	40 (51)	118 (39)	
Missing data	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	
Did the condom break or come off?	20 (26)	19 (26)	15 (19)	22 (28)	76 (25)	
No						.025[b]
Yes	7 (9)	3 (4)	14 (18)	18 (23)	42 (14)	
Not applicable	49 (64)	51 (70)	48 (62)	39 (49)	187 (61)	
How often was a condom used in the previous 3 months?						
Never	16 (21)	19 (26)	12 (16)	9 (11)	56 (18)	.137
Almost never	6 (8)	5 (7)	5 (6)	5 (6)	21 (7)	
Sometimes	24 (32)	17 (23)	23 (30)	16 (20)	80 (26)	
Almost always	26 (34)	27 (37)	29 (38)	30 (38)	112 (37)	
Always	3 (4)	4 (5)	8 (10)	14 (18)	29 (10)	
Do not know/missing data	1 (1)	1 (1)	0 (0)	5 (6)	7 (2)	

NOTE. Data are no. (%) of subjects, unless otherwise indicated. GED, general educational development certificate; SD, standard deviation.

[a] Exact χ^2 or nonparametric Kruskal-Wallis test for differences among treatment arms. When statistically significant, additional 2-sided pairwise tests were performed. Missing data, not applicable, and do not know categories were excluded from P value calculations.

[b] P = .488 for doxycycline therapy arm versus doxycycline + tinidazole therapy arm; P = .810 for azithromycin therapy arm versus azithromycin plus tinidazole therapy arm.

Prevalence of Pathogens at Baseline

The distribution of pathogens detected at baseline is shown in Figure 2. The prevalence of chlamydia was 43%, whereas the prevalence of *M. genitalium* was 31%. *T. vaginalis* was detected in 13% of participants (in urine or swab samples). None of the 3 pathogens were identified in 29% of participants. Sixteen percent of men had multiple pathogens detected, with the most common combination being *C. trachomatis* and *M. genitalium* (8%). No significant differences among treatment arms were detected with respect to the proportion of patients who tested positive for chlamydia (P = .35), *M. genitalium* (P = .96), trichomonas (P = .66) or with respect to the distribution of gram stain PMNs (P = .77).

Efficacy Response by Study Visit

In the MITT population, in which participants who were lost to follow-up (ie, unevaluable) were counted as having experienced treatment failure, clinical cure rates at the first follow-up visit were 74.5% for doxycycline-containing regimens combined and 68.6% for azithromycin-containing regimens combined (Table 2). The

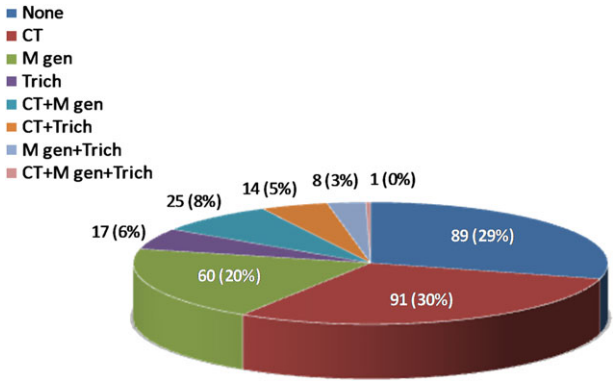

Figure 2. Prevalence of pathogens at baseline.

addition of tinidazole to either regimen did not benefit clinical cure rates. As of the final study visit, cumulative cure rates were 49% for doxycycline-containing regimens and 43.6% for azithromycin-containing regimens. The primary hypotheses comparing doxycycline versus doxycycline plus tinidazole ($P = .34$, 1-sided) and azithromycin versus azithromycin plus tinidazole ($P = .12$, 1-sided) were both nonsignificant. There were no significant differences among any of the 4 treatment arms. Results for the per protocol population were consistent with those for the MITT population.

Of the 82 individuals defined as having experienced clinical failure at the final study visit, 53 (65%) of 82 were defined as such solely on the basis of a urethral smear showing >5 PMNs. If these participants were classified as having experienced cure, there would still be no difference in the efficacy of the treatment arms.

Microbiological Efficacy

The 4 treatment arms differed significantly in the proportions of participants with chlamydial infection at baseline who had negative results after treatment ($P = .017$) (Table 3). The chlamydia clearance rate was 94.8% (55 of 58 participants) for those who received doxycycline with or without tinidazole and was 77.4% (41 of 53) for those who received azithromycin with or without tinidazole ($P = .011$, 2-sided).

The 4 treatment arms also differed significantly with respect to the proportion of participants with *M. genitalium* infection after treatment of participants who had positive results at baseline ($P = .008$). The *M. genitalium* clearance rate was 30.8% (12 of 39 participants) for those who received doxycycline with or without tinidazole and 66.7% (30 of 45) for those who received azithromycin with or without tinidazole ($P = .002$, 2-sided).

Only 1 (5%) of 20 tinidazole-treated participants with trichomonas (detected in urine or swab samples) at baseline had results that remained positive for this infection at follow-up. Among those participants not receiving specific treatment for trichomonas, 5 (31%) of 16 had PCR results that were positive for this pathogen at their follow-up visits. Thus, 11 (69%) of 16 men who had *T. vaginalis* detected at baseline and did not receive tinidazole had apparent spontaneous resolution of the infection (confirmed in urine and swab samples). Of these participants, 8 (73%) of 11 had cleared the infection at the first

Table 2. Efficacy Response by Study Visit for Modified Intent-to-Treat Population

Variable	Doxycycline therapy arm ($n = 76$)	Doxycycline + tinidazole therapy arm ($n = 73$)	Azithromycin therapy arm ($n = 77$)	Azithromycin + tinidazole therapy arm ($n = 79$	All participants ($n = 305$)
Follow-up visit 1	10 (13)	7 (10)	8 (10)	8 (10)	33 (11)
Clinical failure					
Clinical cure	57 (75)	54 (74)	52 (68)	55 (70)	218 (71)
Unevaluable	9 (12)	12 (16)	17 (22)	16 (20)	54 (18)
Follow-up visit 2	22 (29)	17 (23)	24 (31)	19 (24)	82 (27)
Clinical failure					
Clinical cure	22 (29)	24 (33)	19 (25)	25 (32)	90 (30)
Unevaluable	22 (29)	25 (34)	26 (34)	27 (34)	100 (33)
Treatment failure at visit 1	10 (13)	7 (10)	8 (10)	8 (10)	33 (11)
Cumulative efficacy outcome[a]	32 (42)	24 (33)	32 (42)	27 (34)	115 (38)
Clinical failure					
Clinical cure	36 (47)	37 (51)	30 (39)	38 (48)	141 (46)
Unevaluable	8 (11)	12 (16)	15 (19)	14 (18)	49 (16)
Exact 95% CI for cure rate	40.8–64.2	37.4–61.3	20.8–50.7	40.4–63.3	

NOTE. Data are no. (%) of subjects, unless otherwise indicated. CI, confidence interval. $P > .05$ for cure rate.

[a] Subjects who met the criteria for clinical failure at any visit were discontinued from the study and added to the cumulative failures and those who did not return for any follow-up (unevaluable) were counted as treatment failures. Therefore the number cured for the cumulative efficacy outcome was the total number of subjects minus treatment failures minus those who did not return for any follow-up (unevaluable).

Table 3. Microbiologic Cure Rate

Last available result for subjects who were positive at baseline	Doxycycline therapy arm	Doxycycline + tinidazole therapy arm	Azithromycin therapy arm	Azithromycin + tinidazole therapy arm	All participants	P[a]
Chlamydia	0	3	7	5	15	
Positive						.02[c]
Negative	34	21	19	22	96	
Missing data	4	4	3	9	20	
Prevalence (exact 95% CI)[b]	0 (0–10.3)	12.5 (2.7–32.4)	26.9 (11.6–47.8)	18.5 (6.3–38.0)		
Trichomonas in swab/urine samples[d]	3	0	2	1	6	
Positive						.35[e]
Negative	6	9	5	4	24	
Missing	2	3	2	3	10	
Prevalence (exact 95% CI)[b]	33.3 (7.5–70.1)	0 (0–33.6)	28.6 (3.7–71.0)	20.0 (0.5–71.6)		
Mycoplasma genitalium	16	11	9	6	42	
Positive						.005[f]
Negative	5	7	13	17	42	
Missing data	1	4	3	2	10	
Prevalence (exact 95% CI)[b]	76.2 (52.8–91.8)	61.1 (35.8–82.7)	40.9 (20.7–63.7)	26.1 (10.2–48.4)		

NOTE. AZI, azithromycin; CI, confidence interval; DOX, doxycycline; T, tinidazole.

[a] χ^2 of overall group effect (DOX vs DOX + T vs AZI vs AZI + T).

[b] Missing values excluded from the denominator of prevalence (%) calculations.

[c] P values for subsequent a priori specified pairwise comparisons: DOX vs DOX + T, $P = .97$ (1-sided); AZI vs AZI + T, $P = .26$ (1-sided); (DOX, DOX + T) vs (AZI, AZI + T), $P = .01$ (2-sided); [DOX, AZI] vs. [DOX + T, AZI + T], $P = .59$ (2-sided).

[d] All subjects were tested for trichomonas at baseline using tests performed on both swab and urine samples with results that were 93% concordant. Subjects were considered to be positive for infection at baseline if they had positive results on either test. Those subjects who were positive at baseline underwent follow-up testing of both urine and swab samples, which had results that were 100% concordant at the final follow-up visit.

[e] No subsequent pairwise comparisons performed, because the overall group effect was nonsignificant as specified a priori.

[f] P values for subsequent a priori specified pairwise comparisons: DOX vs DOX + T, $P = .24$ (1-sided); AZI vs AZI + T, $P = .18$ (1-sided); (DOX, DOX + T) vs (AZI, AZI + T), $P = .002$ (2-sided); [DOX, AZI] vs [DOX + T, AZI + T], $P = .19$ (2-sided).

follow-up visit, and 3 (27%) of 11 had cleared the infection by the second follow-up visit. Interim use of metronidazole could only be documented for 1 of these individuals. Among those participants in whom *T. vaginalis* infection resolved and in whom it was the only pathogen detected, 8 (72.7%) of 11 met the definition of clinical cure of NGU. None of the 4 participants who failed to clear *T. vaginalis* in the doxycycline or azithromycin only arms were deemed to have experienced clinical cure.

Participant Adherence to the Protocol

Only 2% of participants reported taking antibiotics other than the study drugs during follow-up. At the first follow-up visit, 61% of participants were adherent to therapy, which was defined as taking at least 80% of the medications, as determined on the basis of pill count. No significant differences among study groups were detected with respect to medication adherence.

At the first follow-up visit, the median number of sexual partners and median number of new sexual partners reported since the baseline visit were 1.0 and 0, respectively. There were no significant differences among the 4 treatment arms with respect to sexual behavior with the exception of frequency of receptive oral sex ($P = .009$). The pairwise comparison between therapy with azithromycin only and therapy with azithromycin plus tinidazole was statistically significant ($P = .01$). At the second follow-up visit, the median number of sexual partners and median number of new sexual partners reported since the last visit were 1.0 and 0, respectively. There were no significant differences among the 4 treatment arms with respect to sexual behavior. At the first follow-up visit, 75% of participants who reported having sex since the last visit reported always using a condom. Seventy-seven percent stated that they had used a condom during their most recent sexual encounter. At the second follow-up visit, 57% of participants who had had sex since the previous visit reported always using a condom. Seventy-one percent stated that they had used a condom during their most recent encounter. There were no significant differences among the 4 treatment arms with respect to frequency of condom use or condom use for the most recent sexual encounter at either follow-up visit.

Adverse Events

Study drugs were well tolerated, with similar rates of adverse events reported for the 4 study arms. The most frequently reported adverse events were nausea, vomiting, abdominal pain, diarrhea, and taste abnormality (Table 4). Only 1 severe (grade 3) event, diarrhea, was reported.

Table 4. Adverse Events at the Participant Level

Adverse event	No. (%) of participants				*P*
	Doxycycline therapy arm	Doxycycline + tinidazole therapy arm	Azithromycin therapy arm	Azithromycin + tinidazole therapy arm	
Nausea	3 (4)	4 (6)	0	4 (5)	.248
Vomiting	4 (5)	2 (3)	0	0	.054
Abdominal pain	6 (8)	5 (7)	3 (4)	5 (6)	.770
Diarrhea	0	3 (4)	3 (4)	7 (9)	.057
Taste abnormality	0	6 (8)	0	4 (5)	.009

DISCUSSION

Nongonoccoccal urethritis is a common clinical syndrome. Recommended initial treatment regimens primarily target *C. trachomatis* as the etiology, although the contributions of other pathogens, including *T. vaginalis* and *M. genitalium,* have been increasingly reported [5, 6, 12–19]. In one study, trichomonas was nearly as common as chlamydia (17.3% vs 19.6%) [6]. Despite this, current recommendations are to include antitrichomonal therapy only for men with persistent NGU [9]. In terms of *M. genitalium,* Mena et al [13] found a prevalence of 21% among men with symptomatic NGU. The optimal therapy for *M. genitalium* remains unclear, because treatment failure has been reported for both doxycycline and azithromycin therapy [20]. Interestingly, older studies found that NGU caused by chlamydia responded significantly better to tetracyclines than did cases of NGU in which no chlamydia was found [21, 22].

In our study, tinidazole did not enhance the clinical cure rates of conventional therapy for NGU. This finding may be attributable to the lower-than-anticipated prevalence of trichomonas among study participants and the high rate of spontaneous regression of trichomonas in the absence of tinidazole. Spontaneous resolution of trichomonas from the urethra has been previously reported [23, 24]. Of note, among those men with trichomonas who received tinidazole, only 1 microbiological failure occurred.

Important findings in our study were the significant differences in the microbiologic cure rates for *M. genitalium* and, especially, *C. trachomatis* following treatment with doxycycline or azithromycin. Azithromycin was significantly more effective against *M. genitalium* than was doxycyline; however, doxycycline therapy offered superior efficacy over azithromycin therapy for chlamydia. Failure to cure *M. genitalium* with both doxycline and azithromycin therapy has been previously documented [7, 25, 26], and one randomized study showed azithromycin therapy to be more efficacious than doxycycline therapy [20]. However, we are unaware of clinical studies that have shown doxycycline to be superior to azithromycin for the treatment of *C. trachomatis.* Clearly, these are important topics for additional study.

In our study, cure rates were lower than those reported by Stamm et al [4]. Reasons for lower clinical cure rates could include the high rate of *C. trachomatis* infection coupled with the lower observed efficacy of azithromycin therapy for this infection in our study, as well as potential re-infections in this high-risk population. Finally, it is possible that there has been a real decrease in response to therapy for NGU over the previous 2 decades. Compared with rates of cure in clinical practice, rates of cure at the final study visit are underestimated, because the majority of clinical cures in our study and in that of Stamm et al [4] were based solely on the persistence of neutrophils and would not have been recognized in the course of usual care, a setting in which test-of-cure gram stains are not routinely performed.

The limitations of our study include the aforementioned lower-than-anticipated prevalence of trichomonas, coupled with spontaneous regression of trichomonas in the absence of tinidazole. A larger sample size, which would have accounted for these factors, may have been desirable. Our study population was largely African American and may not be applicable to a more diverse group of men.

In summary, the addition of tinidazole to doxycycline or azithromycin therapy did not result in higher rates of clinical cure but did effectively eradicate trichomonas. Clinical cure rates were not significantly different between the doxycycline and azithromycin arms. However, doxycycline therapy had significantly better efficacy against Chlamydia, whereas azithromycin therapy was superior for the treatment of *M. genitalium* infection. Based on these data, it may be that management of NGU, and especially of recurrent or persistent NGU, should be guided by an etiologic diagnosis rather than by a syndromic approach.

Acknowledgments

We thank the late Walter Stamm, MD, for the many contributions that he made to the study design and to the field of urethritis. Mission Pharmacal (San Antonio, TX) kindly provided tinidazole for this study.

Financial support. Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases at the

National Institute of Health (DMID contract number N01AI40073C), North Carolina Sexually Transmitted Infections and Topical Microbicides Cooperative Research Center (grant U19-AI31496).

Potential conflicts of interest. All authors: no conflicts.

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